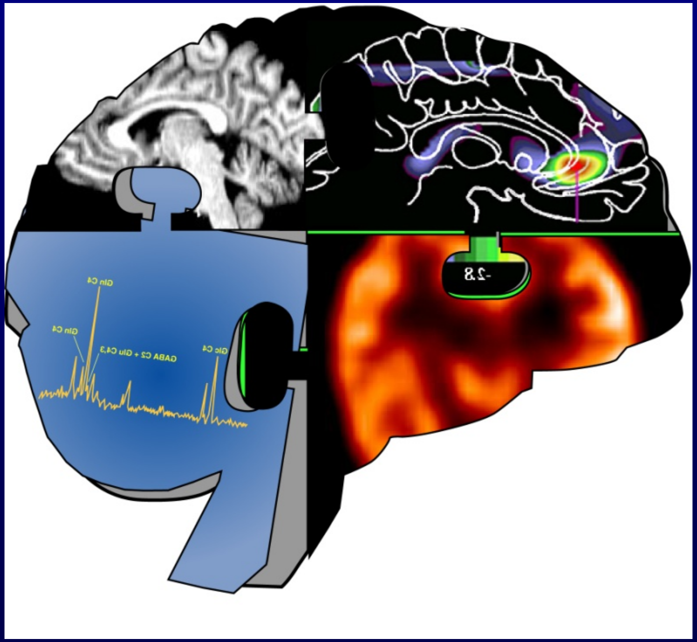
Positron Emission Tomography: Tool to Facilitate Drug Development and to Study Pharmacokinetics



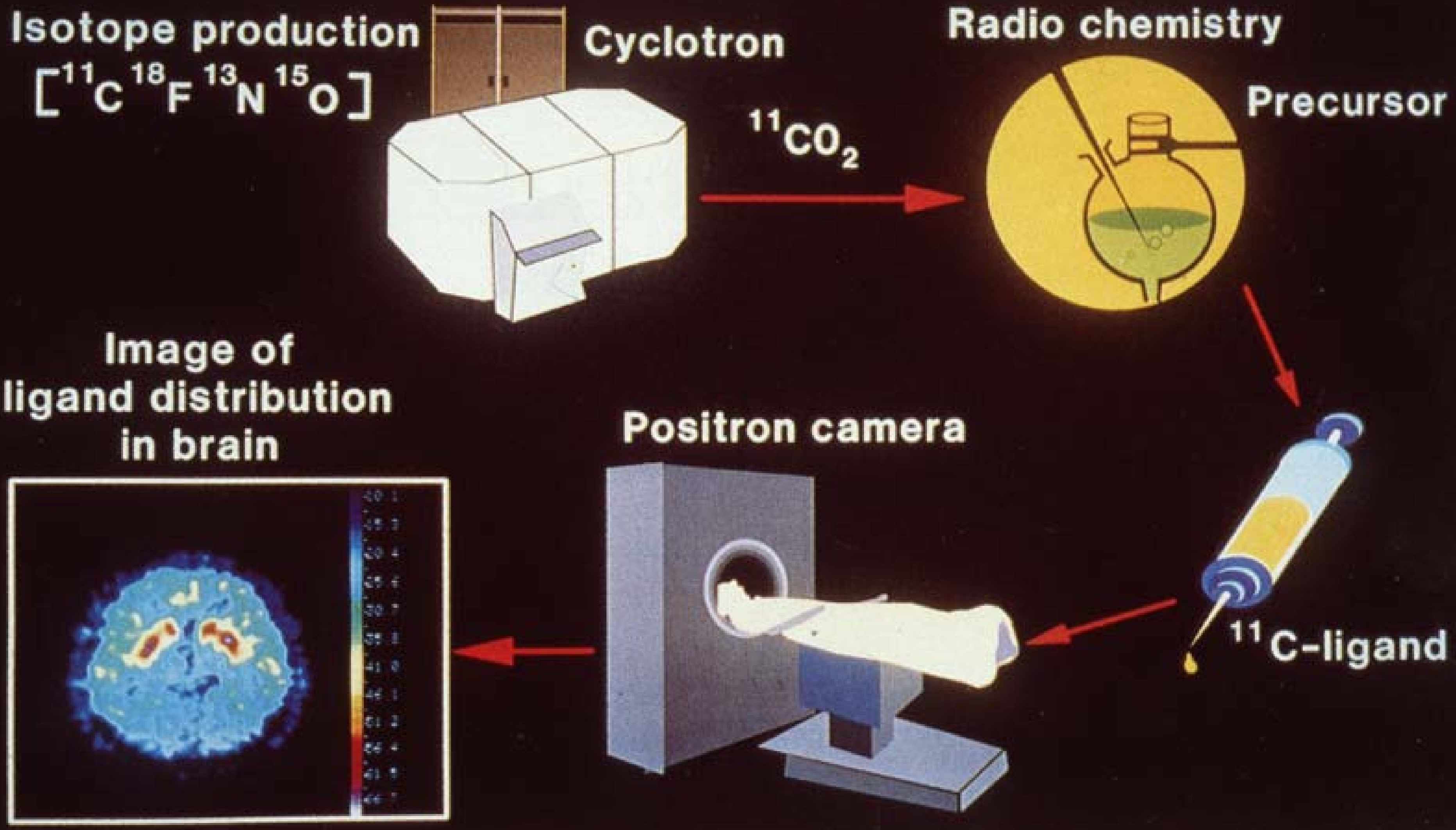
Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Institute Mental Health

October 9, 2008

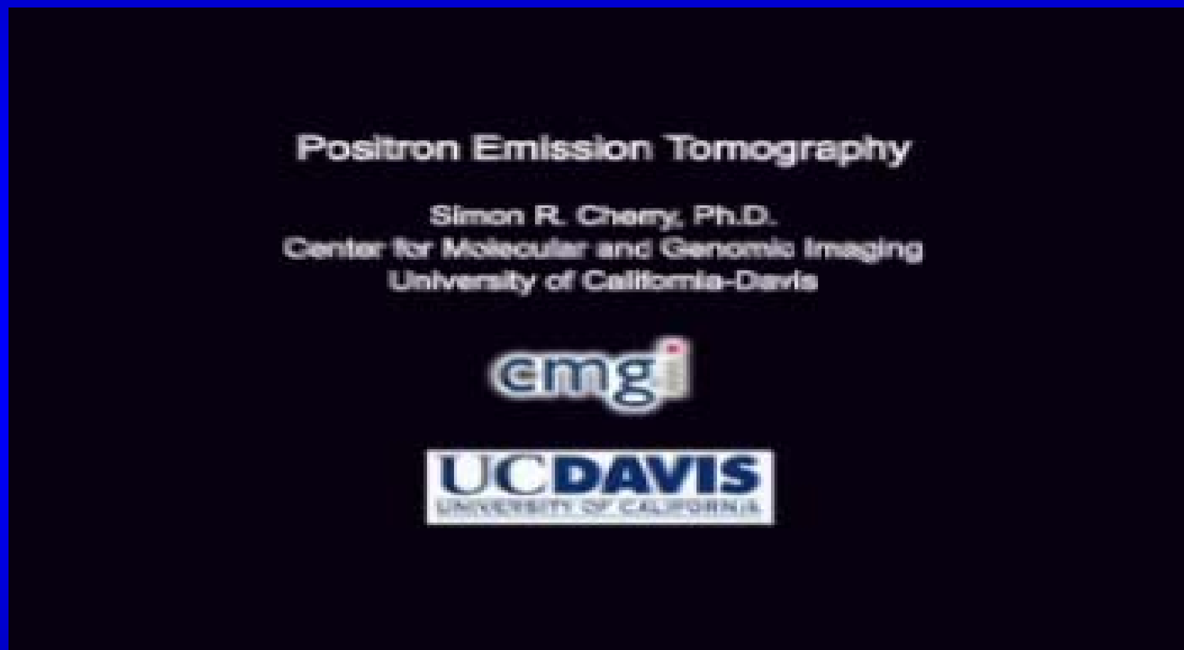
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

Imaging of neuroreceptors by PET



Positron Emission Tomography



PET vs. MRI

	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

Radionuclide (^{11}C): high sensitivity

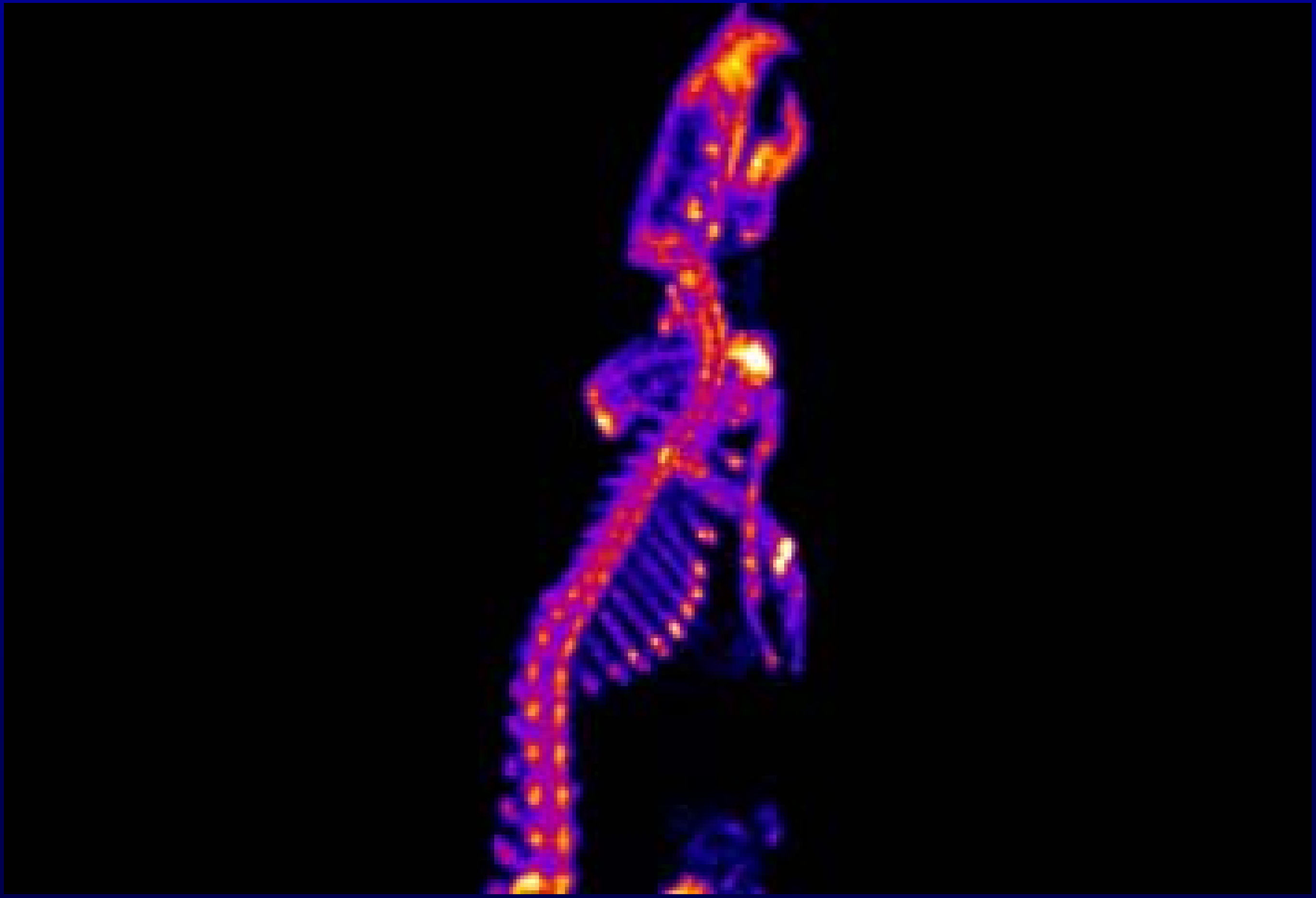
Ligand (raclopride): high selectivity

Radioligand [^{11}C]raclopride: high sensitivity & selectivity

Radioligand = Drug + Radioactivity

1. **Drug administered at tracer doses**
   a) No pharm effects
   b) Labels <1% receptors
   c) Labeled subset reflects entire population
2. **Radioligand disposed like all drugs**
   a) Metabolism & distribution
3. **Radiation exposure**

NIH Rodent PET Camera
^{18}F bone uptake rat

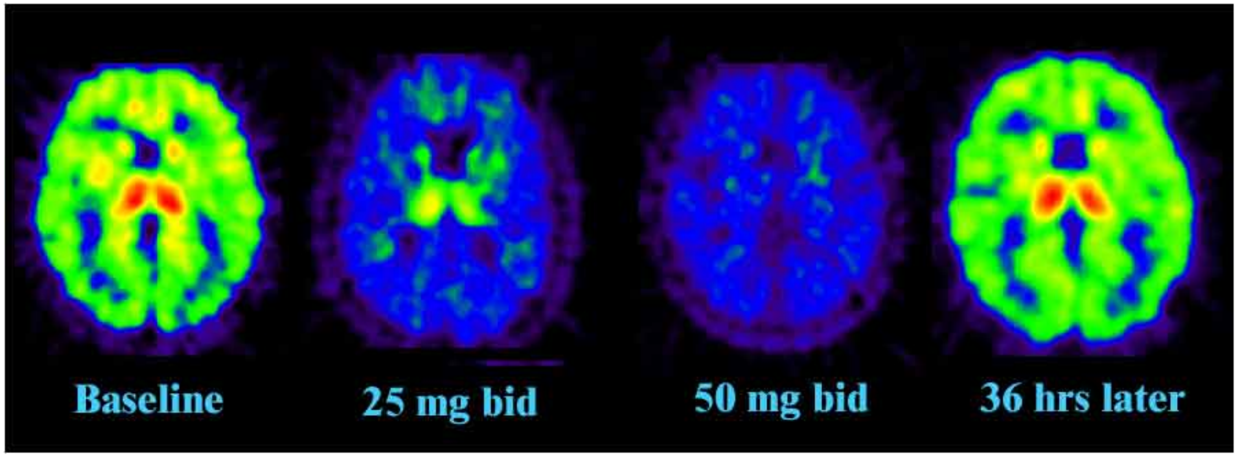


Developed By: Mike Green & Jurgen Seidel

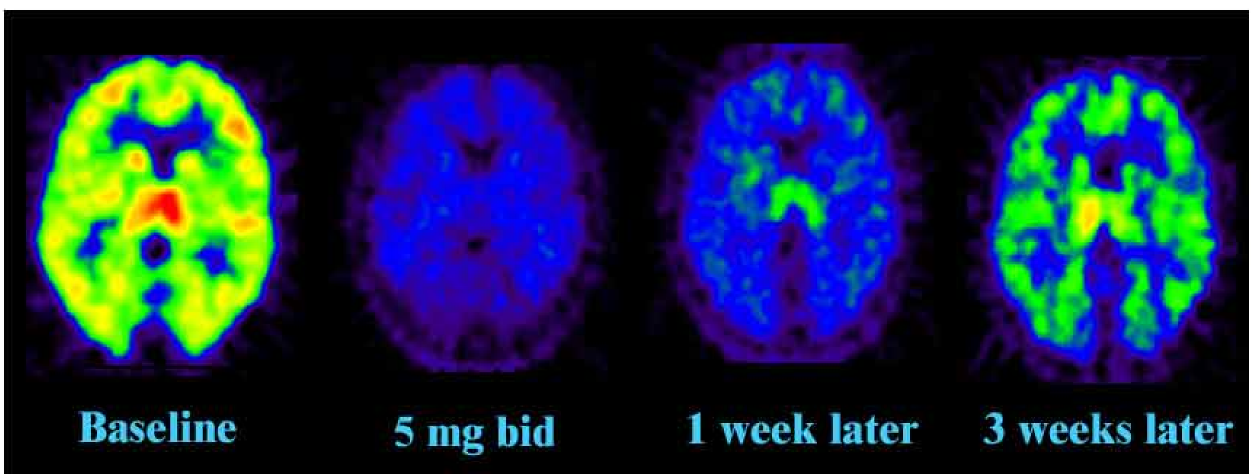
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

Lazabemide blocks [^{11}C]deprenyl binding to monoamine-oxidase-B (MAO-B)



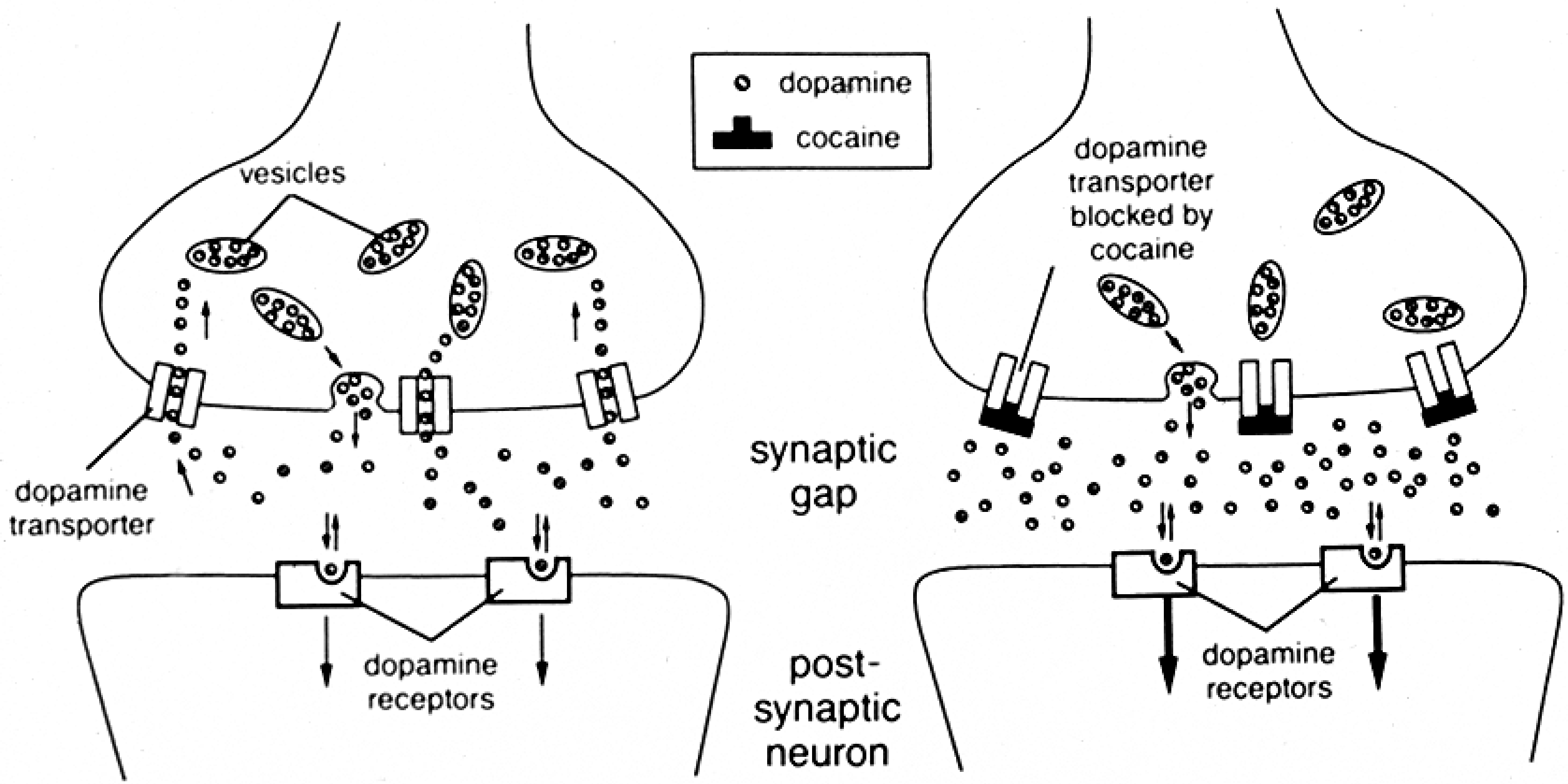
Selegilene is more potent and longer acting than lazabemide



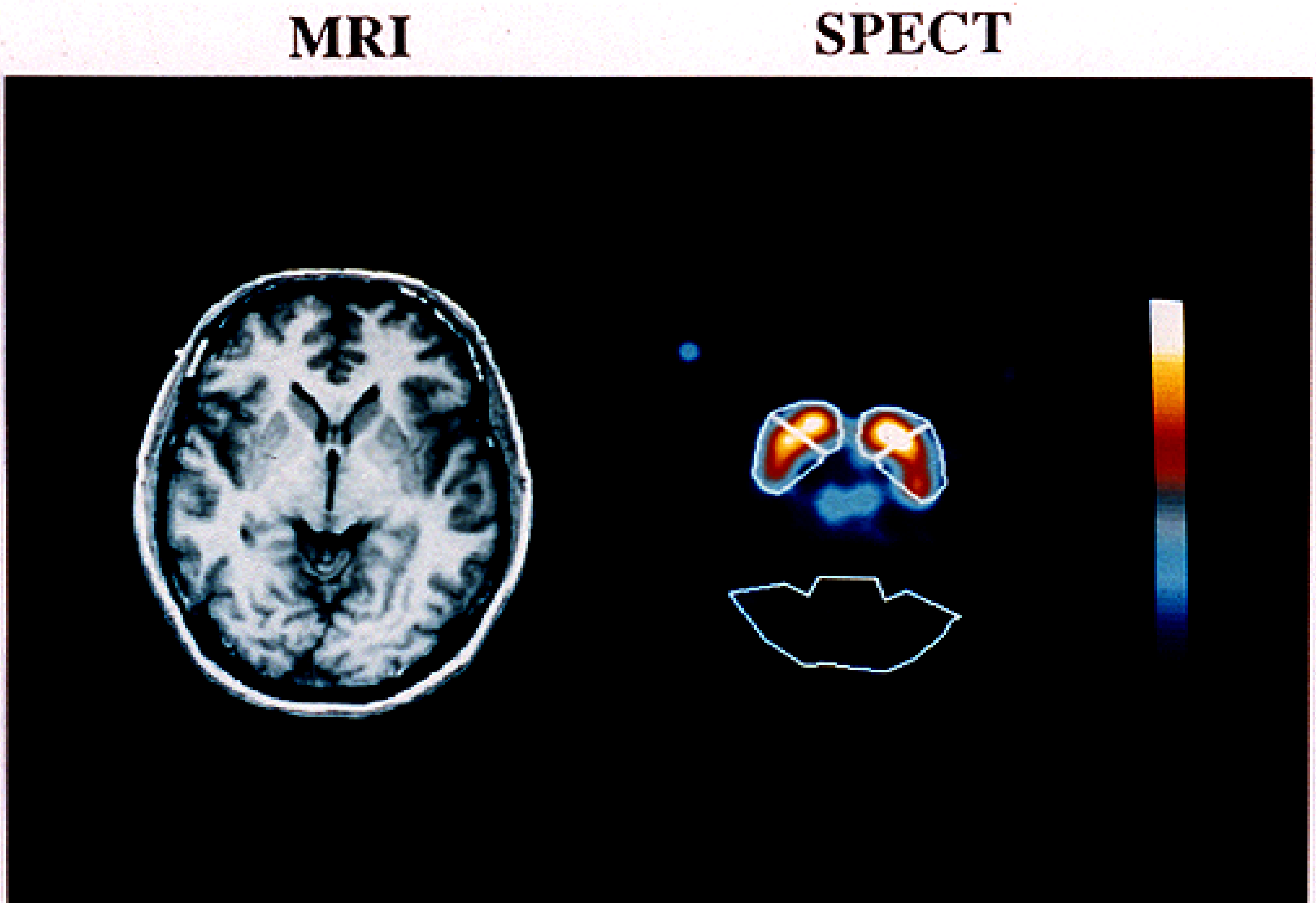
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

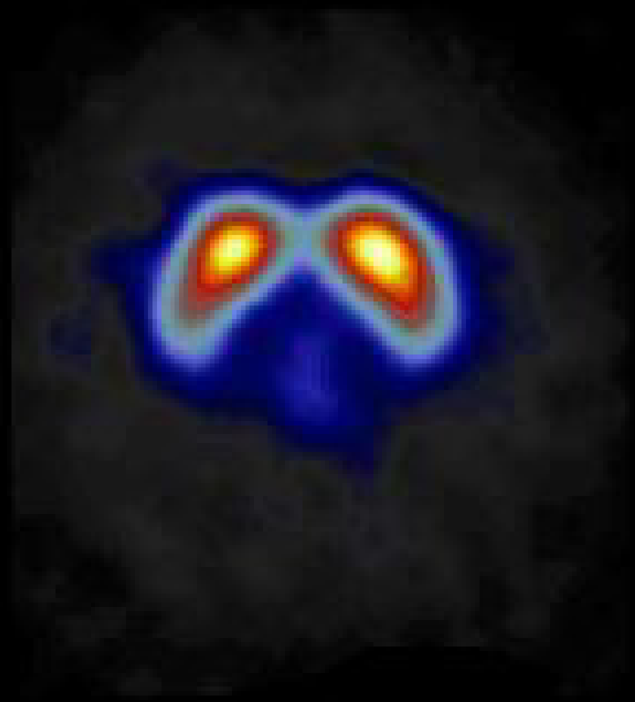
Dopamine Transporter: Located on DA Terminals
Removes DA from Synapse



SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain



^{123}I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease



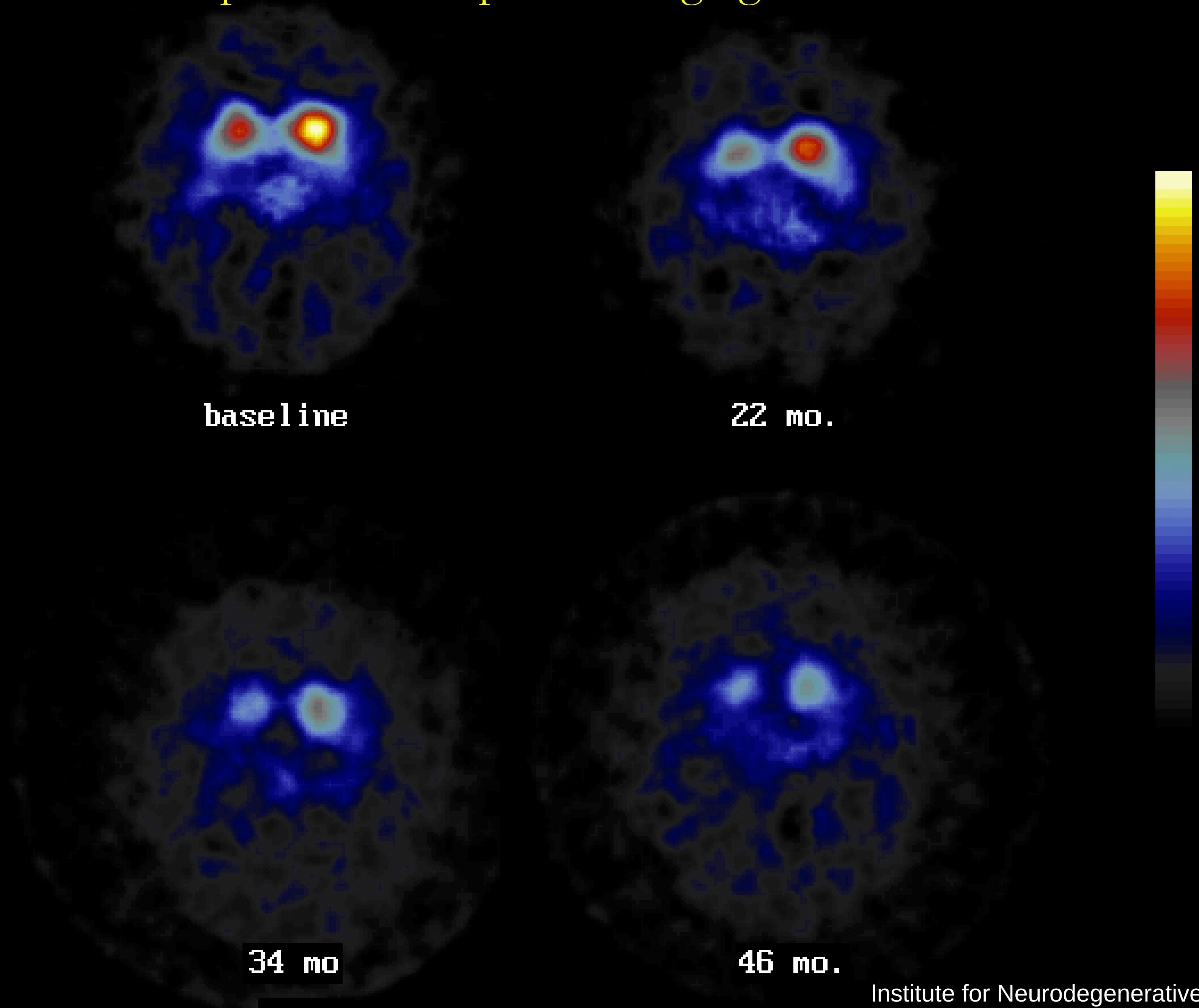
Healthy

Parkinson
Stage 1

PET: Tool in Therapeutic Drug Development

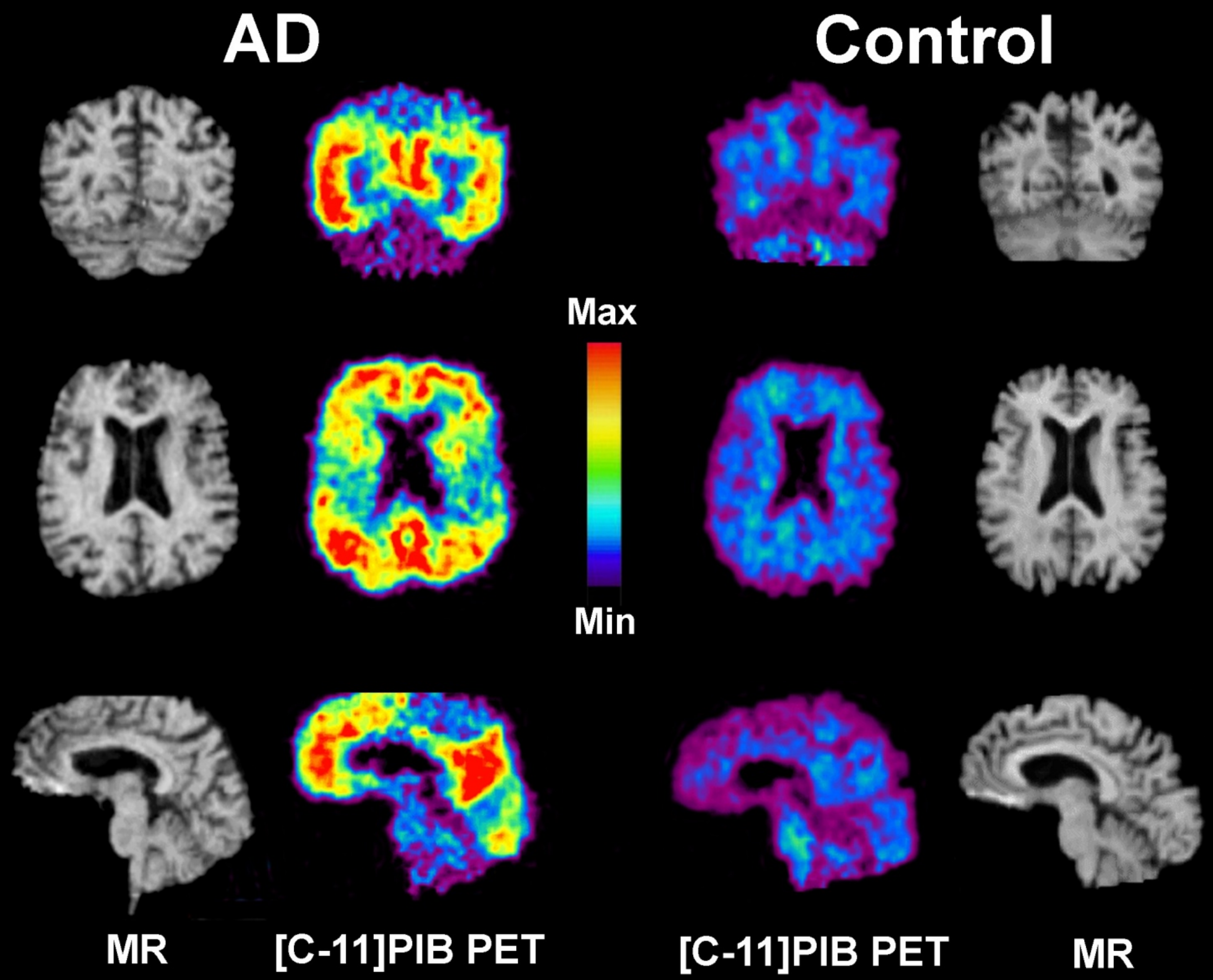
- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

Serial Dopamine Transporter Imaging in a Parkinson Patient



Institute for Neurodegenerative Disorders

PET Imaging of Amyloid: Biomarker for Alzheimer's Disease



University of Pittsburgh
PET Amyloid Imaging Group

PET: Tool in Therapeutic Drug Development

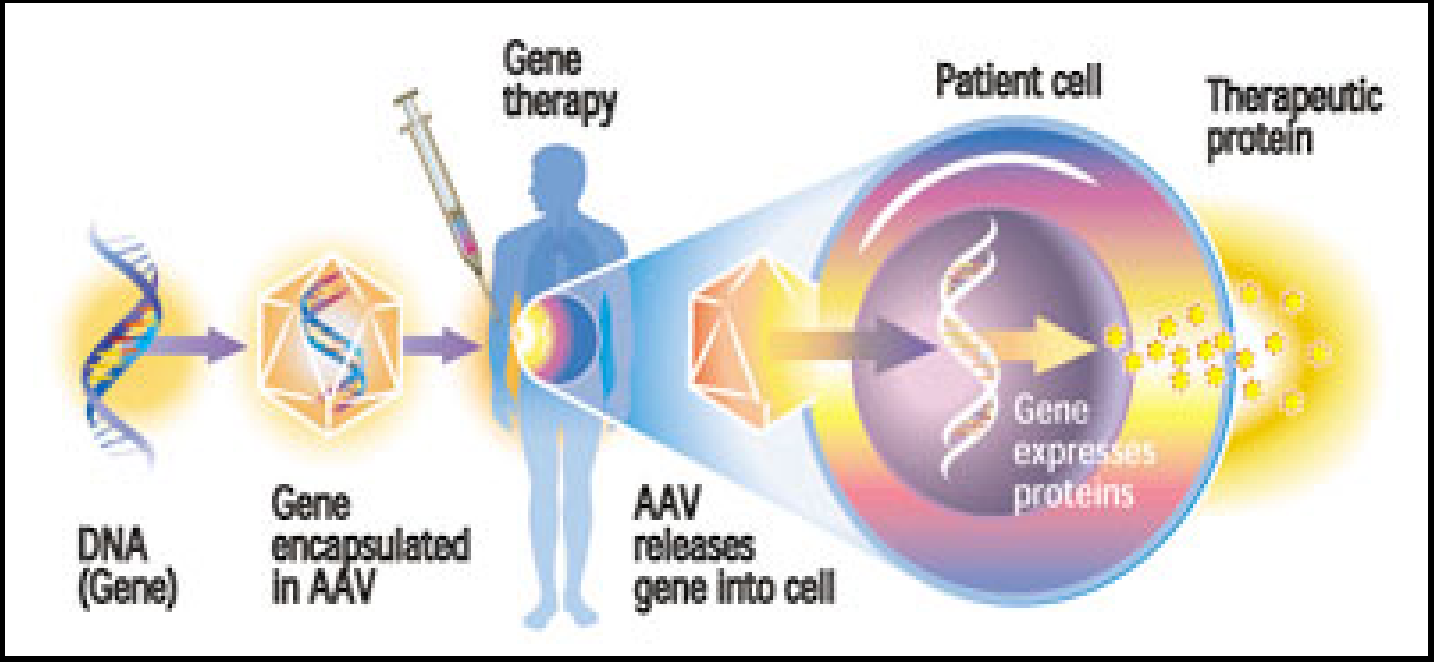
- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

Gene Therapy Using Viral Vectors

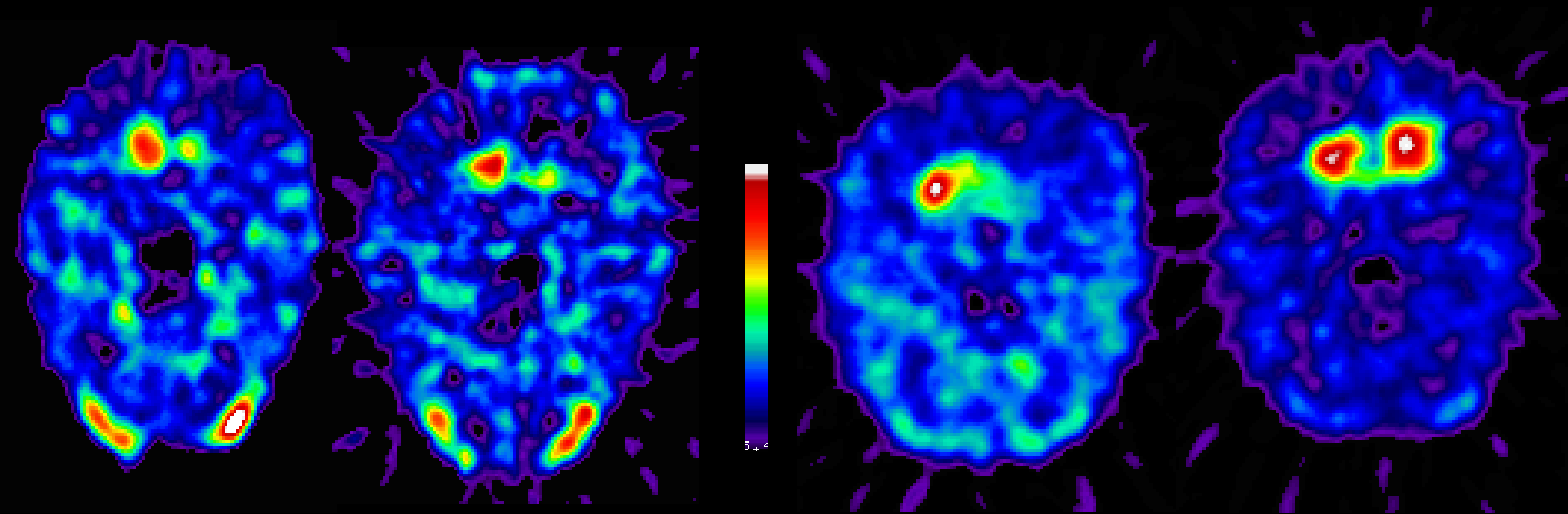
Viral vectors deliver gene
that synthesizes dopamine (DA)

Infuse virus into striatum (target cells)

Target cells express the DA gene



PET Dopamine Imaging in Hemi-Parkinson Monkey:
Monitors gene for DA synthesis in right striatum



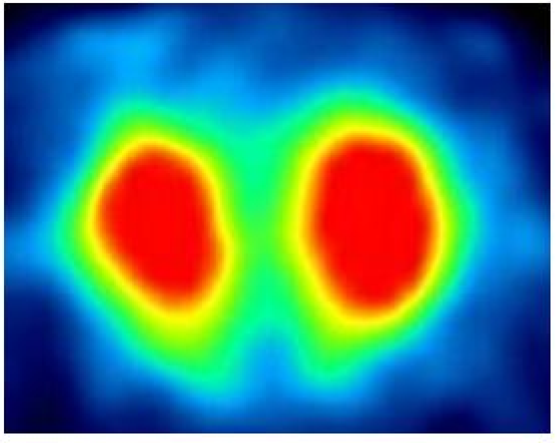
pre post pre post

Control Gene: Lac-Z

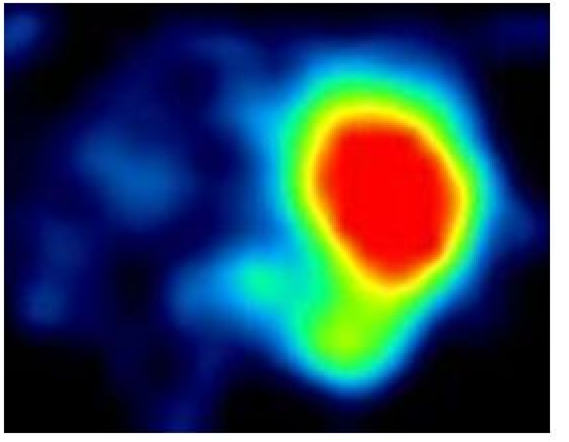
DA Synthesis Gene: AADC

PET Imaging to Monitor Embryonic Stem Cell Treatment of "Parkinson Disease" in Rats

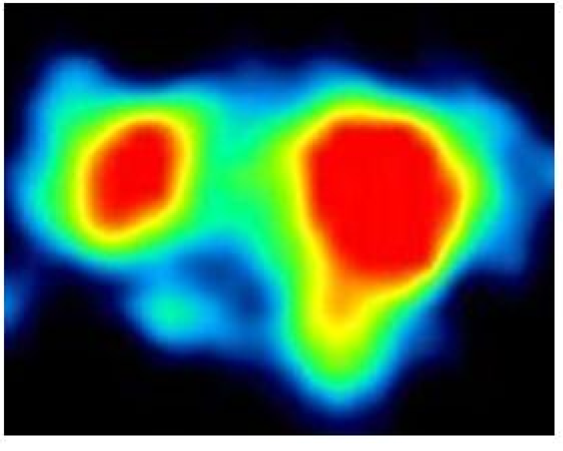
Normal



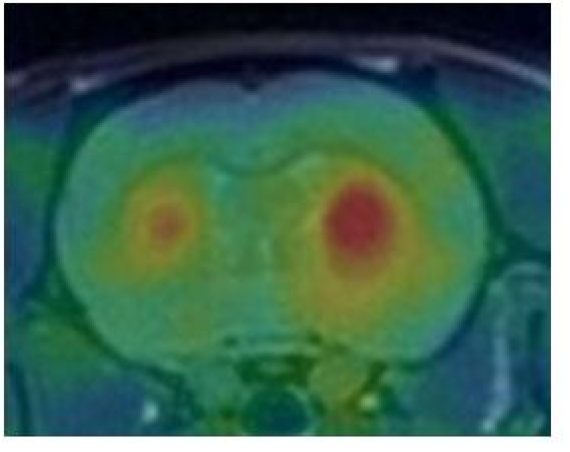
Unilateral Lesion



Embryonic Stem Cells



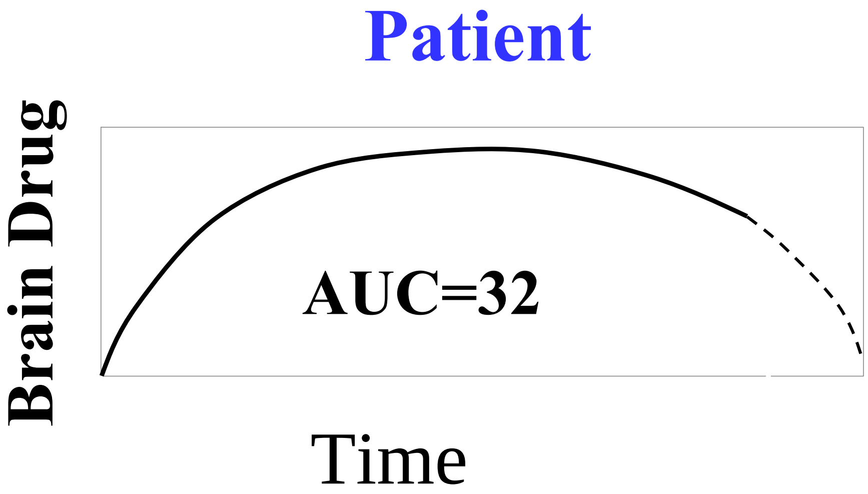
PET & MRI

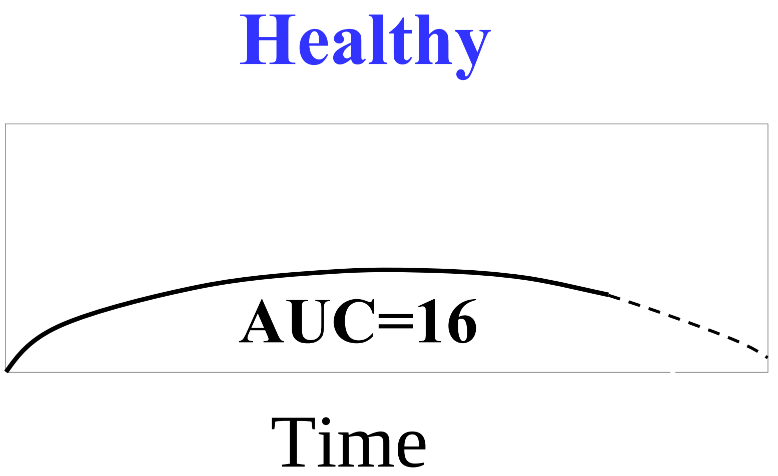


Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

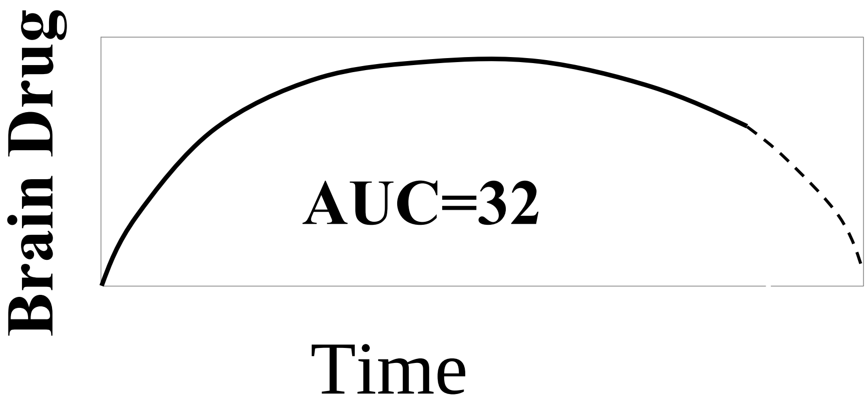
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



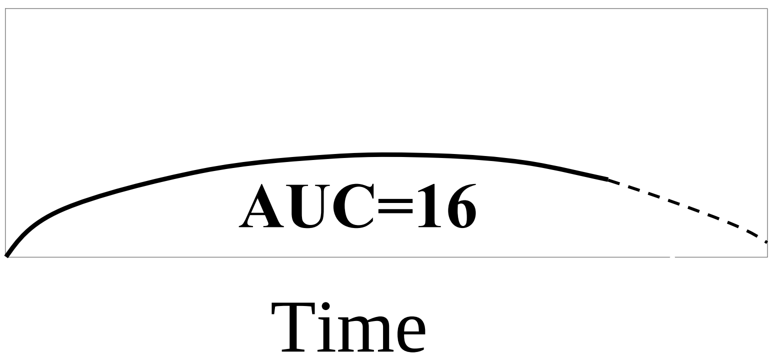


Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Patient

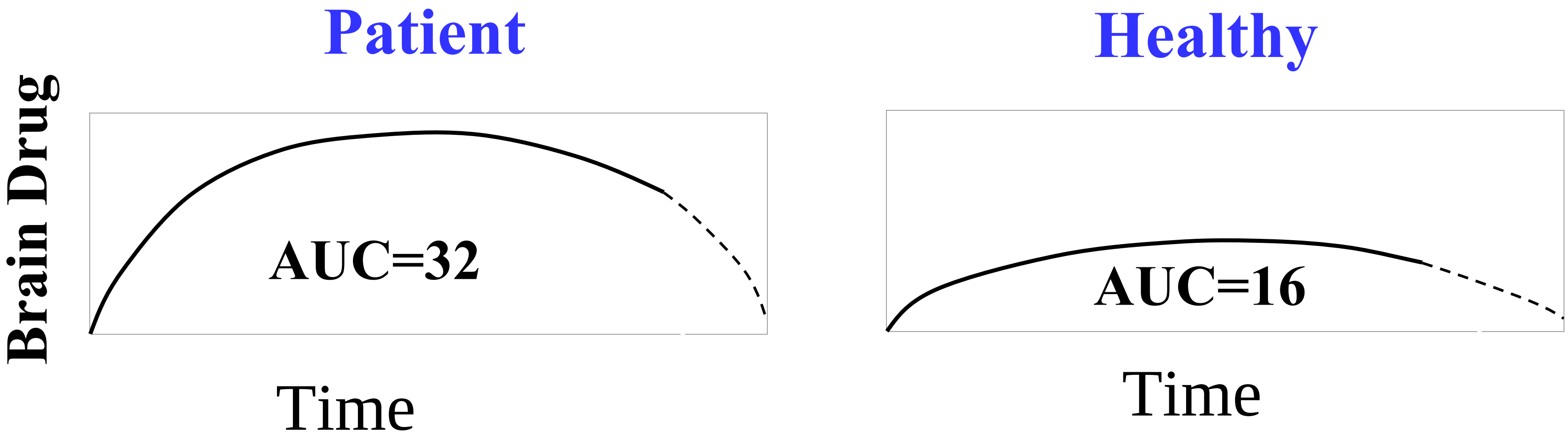


Healthy



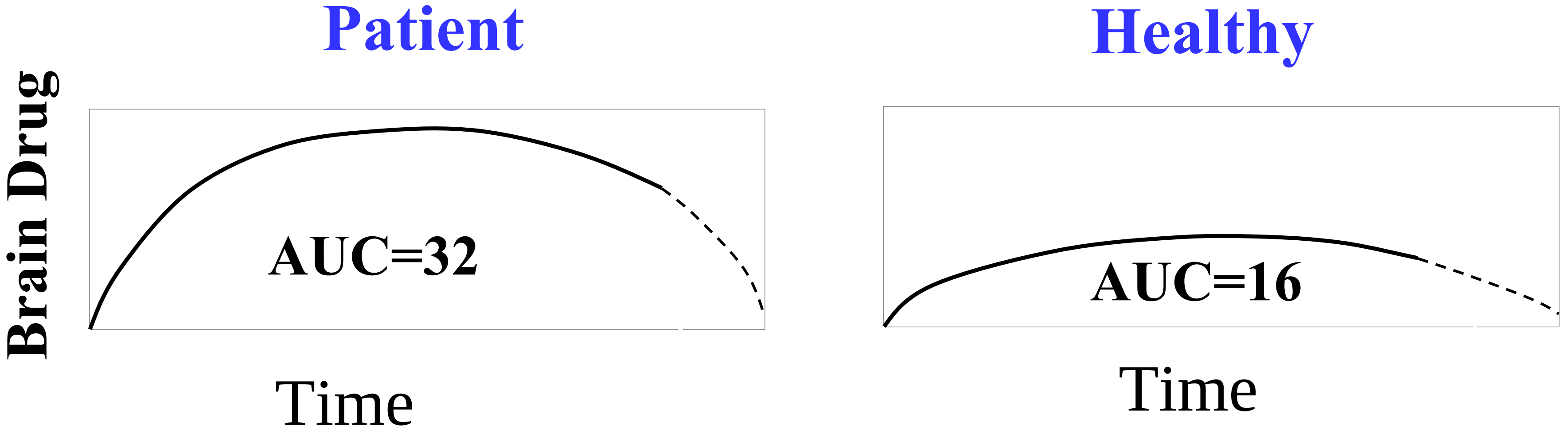
	Patient	Healthy
Inject Activity	20 mCi	10 mCi

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



	Patient	Healthy
Inject Activity	20 mCi	20 mCi

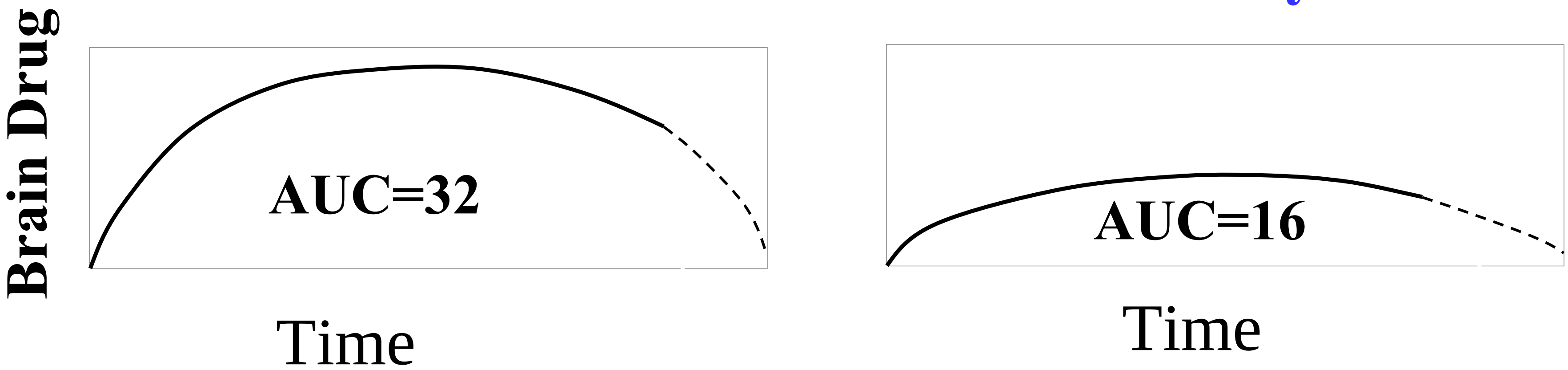
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	50 kg	100 kg

Brain Uptake of [¹⁸F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

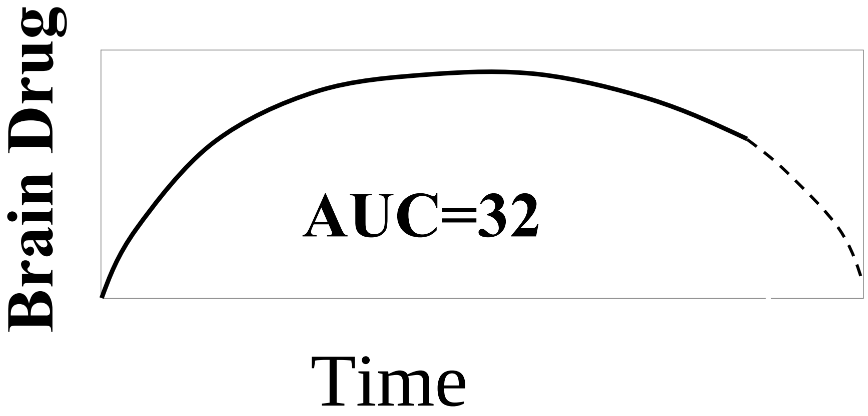
Patient **Healthy**



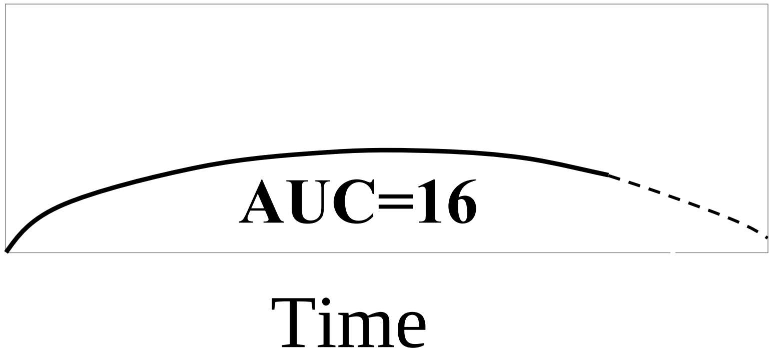
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters

Patient



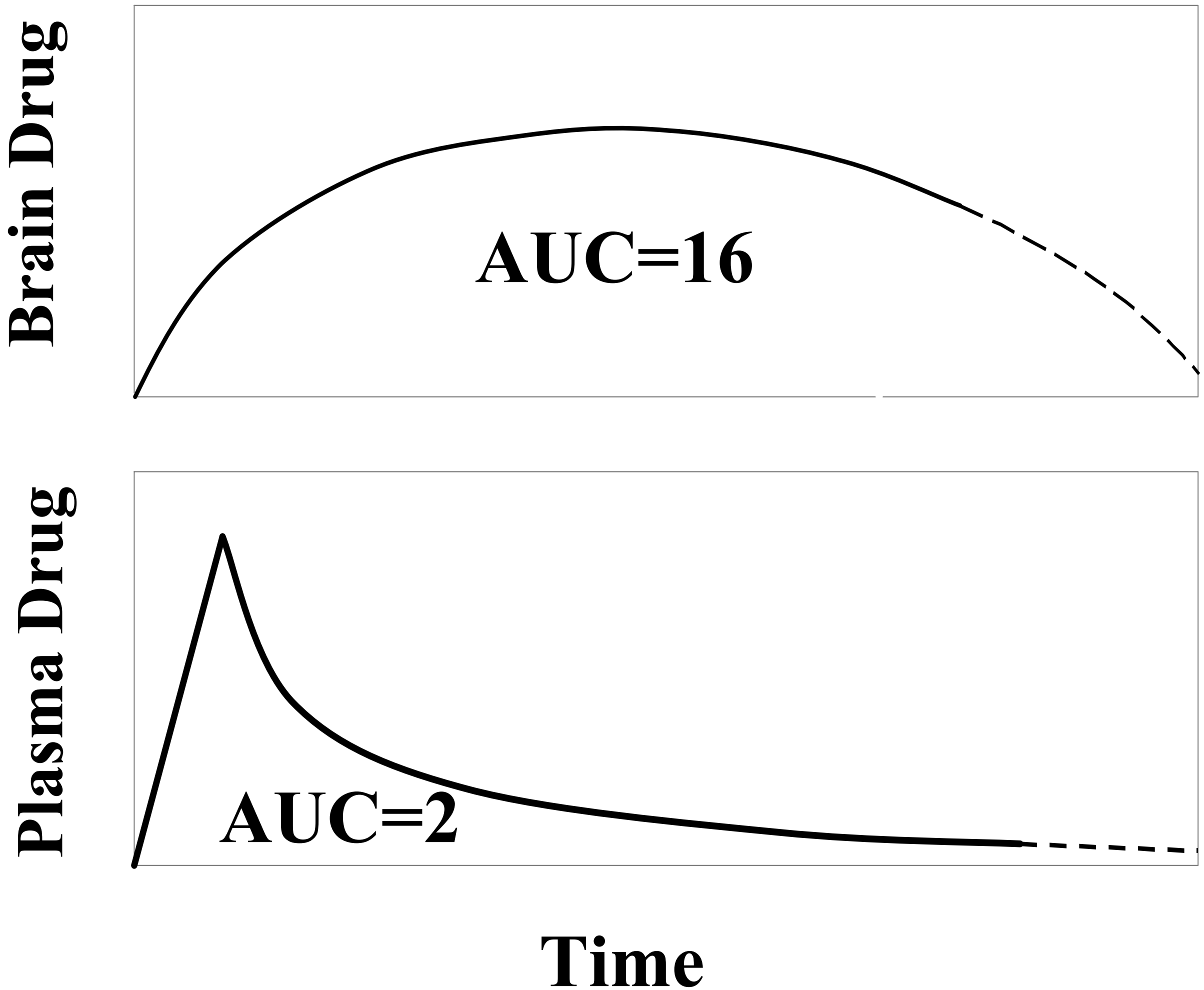
Healthy



	Patient	Healthy
Inject Activity	40 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No

Binding Potential (BP)

BP equals uptake in brain relative to how much activity is delivered in arterial plasma



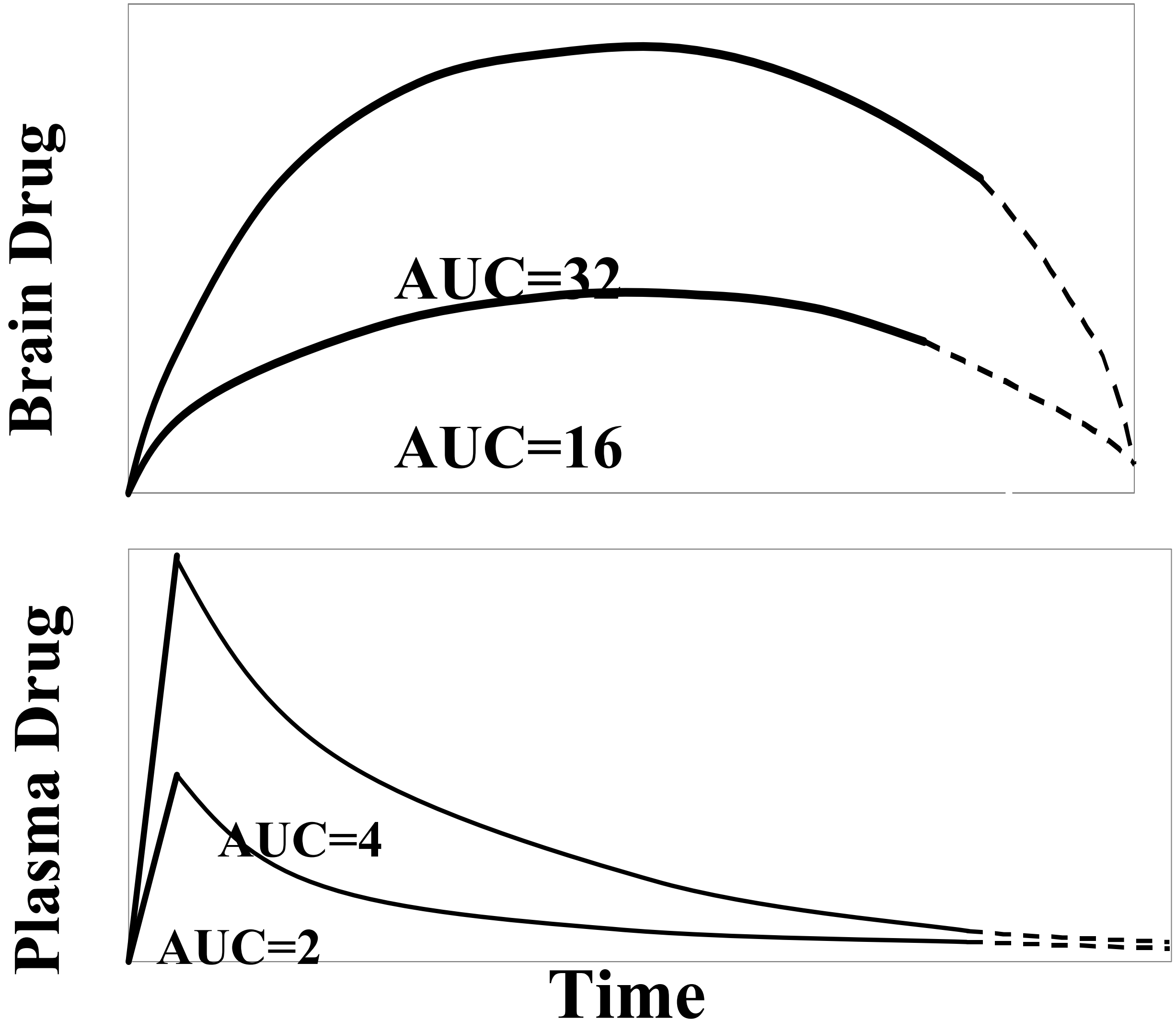
$$BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$BP = \frac{16}{2} = 8$$

Binding Potential: Independent of Injected Dose*

Double Plasma Input =>Double Brain Response

***If ligand does not saturate receptors - i.e. if tracer doses used**



BP 1st Time = $\mathbf{\frac{32}{4} = 8}$

BP 2nd Time = $\mathbf{\frac{16}{2} = 8}$

BP can be calculated from the Area Under Curve (math integral) as well as rate constants (math differential).

From curves of plasma and brain radioactivity over time, estimate rate constants of entry and removal to/from tissue.

$$\boxed{\text{Plasma}} \underset{k_2}{\overset{K_1}{\rightleftarrows}} \boxed{\text{Brain}}$$

$$BP = \frac{K_1}{k_2}$$

Tissue uptake is proportional to density of receptors and the affinity of the drug

Binding Potential

$$BP = \frac{B_{\mathrm{max}}}{K_{\mathrm{D}}} = B_{\mathrm{max}} \times \frac{1}{K_{\mathrm{D}}} = B_{\mathrm{max}} \times \text{affinity}$$

$B_{\mathrm{max}} = \text{receptor density}$

$K_{\mathrm{D}} = \text{dissociation binding constant}$

$\frac{1}{K_{\mathrm{D}}} = \text{binding affinity drug}$

SUMMARY PET KINETICS

- Organ uptake is proportional to receptor density and affinity of drug
- Binding Potential (BP) = density X affinity
- “Drug Exposure” to tissue is AUC of:

  plasma concentration *vs.* time
- “Response” (uptake) of tissue is AUC of:

  tissue concentration *vs.* time

$$BP = \frac{\text{Response}}{\text{Exposure}} = \frac{AUC_{\text{tissue}}}{AUC_{\text{plasma}}}$$

- BP also equals ratio of rate constants of entry and removal to/from tissue

$$BP = \frac{K_1}{k_2}$$

Major Point of PET Pharmacokinetics
(in words)

- Plasma pharmacokinetics provides a limited view of what's happening to drug in plasma.
- PET provides a limited view of what's happening to drug in tissue.
- **Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action – *i.e.*, receptor.**

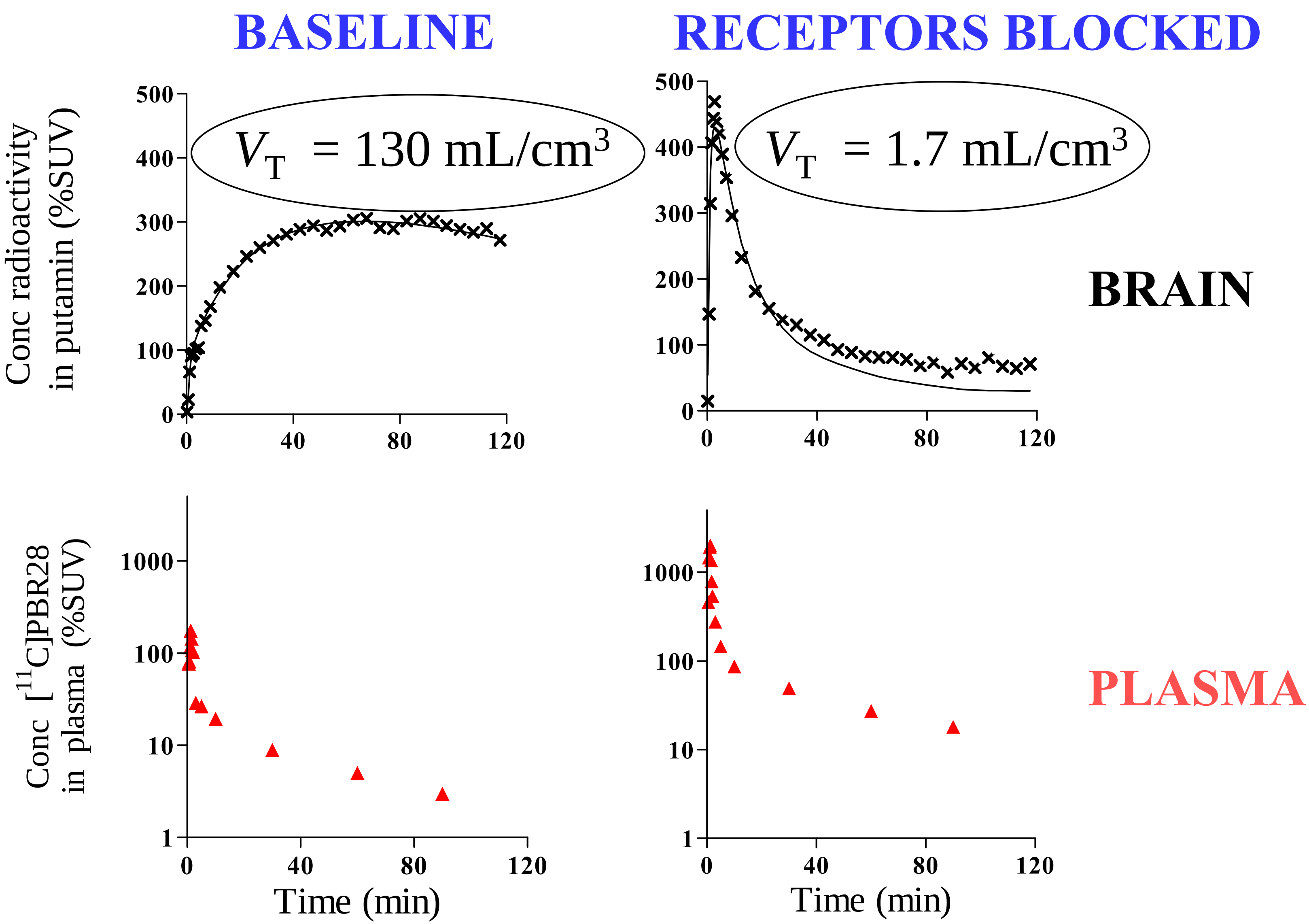
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

“Peripheral” Benzodiazepine Receptor

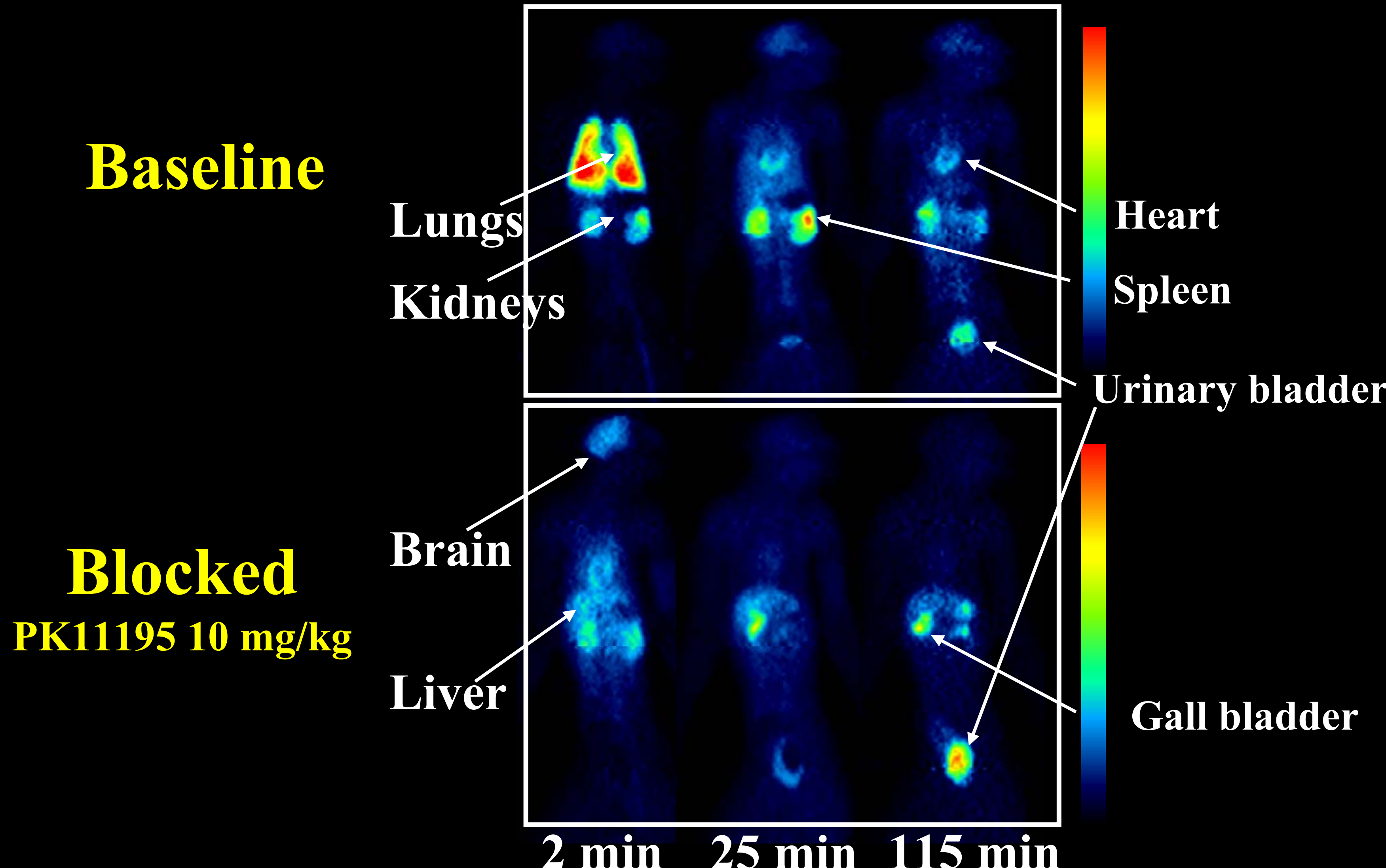
1. Mitochondrial protein highly expressed in macrophages and activated microglia
2. Exists in periphery and brain
3. Multiple potential functions: steroid synthesis, nucleotide transport
4. Distinct from typical benzodiazepine $GABA_A$ receptor in brain
5. Marker for cellular inflammation

Receptor Blockade [^{11}C]PBR28 in Monkey Brain: more radioligand in plasma and brain

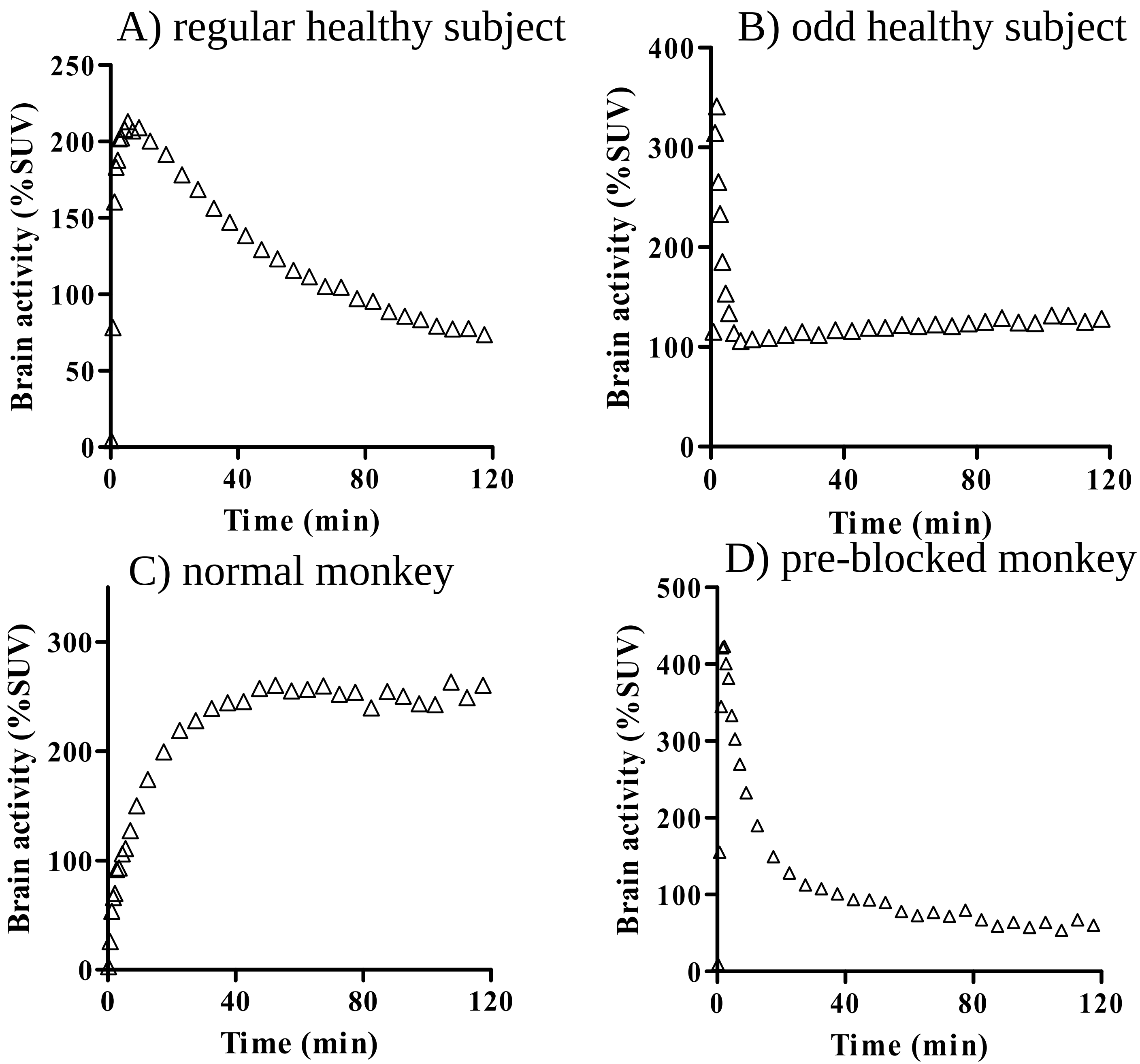


MONKEY WHOLE BODY SCANS [^{11}C]PBR28

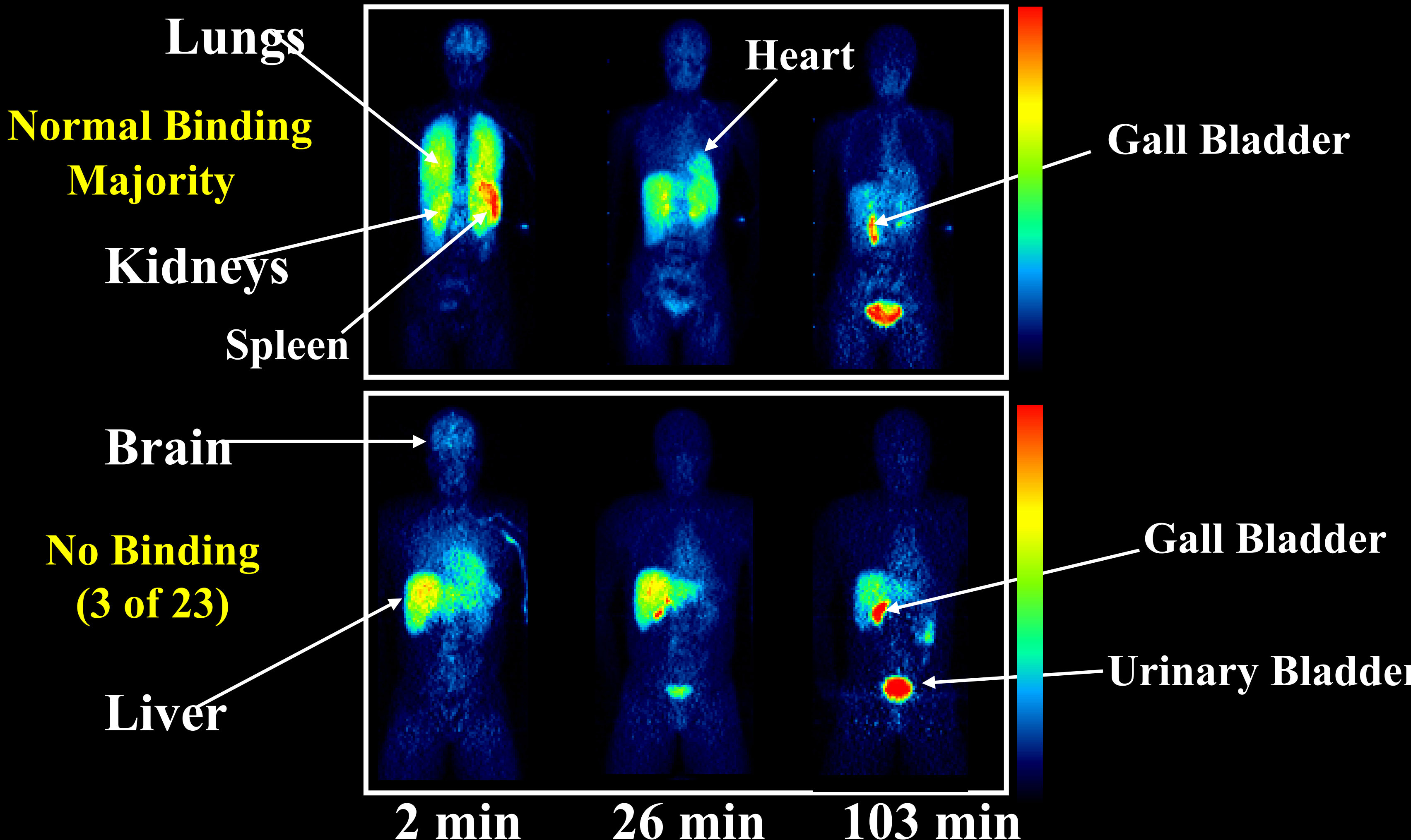
Receptor blockade displaces from lung & kidney
Drives more to metabolism (liver) and exretion (urine)



Human with low uptake is similar to monkey with receptor blockade



Some HEALTHY Subjects May have No Receptor Binding of $[^{11}C]$PBR28



Nonbinders showed a trend of higher plasma $[^{11}C]$PBR28

INFLAMMATION IMAGING
On-going Studies

Neurocysticercosis

Multiple sclerosis

HIV with cognitive impairment

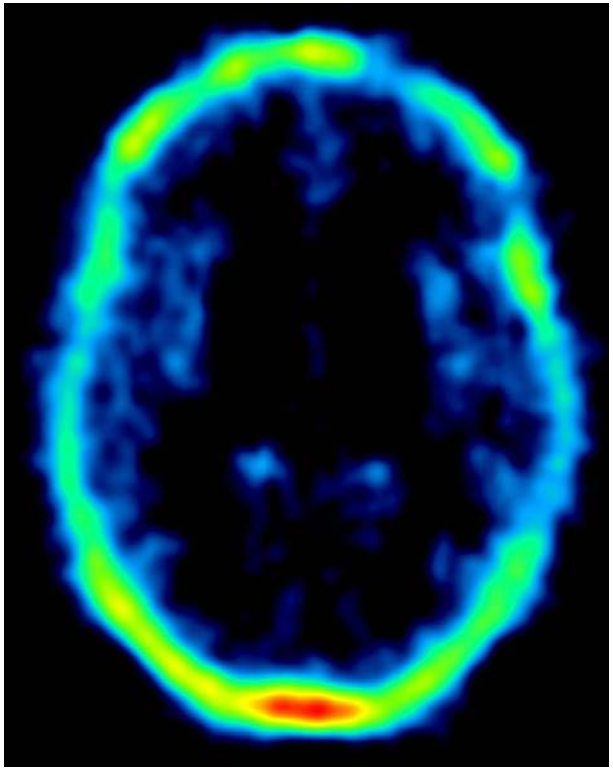
Alzheimer's disease

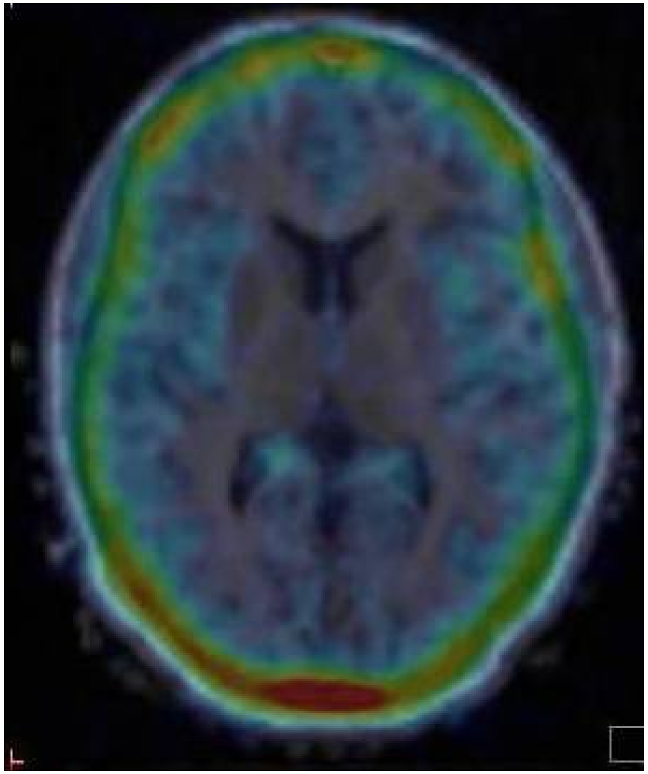
Atherosclerosis

Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

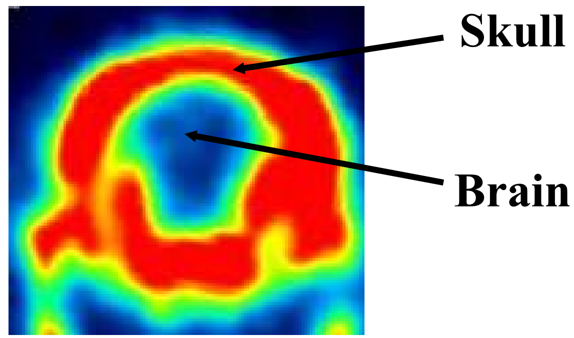
[^{18}F]FCWAY: Defluorination Bone uptake: human skull at 2 h

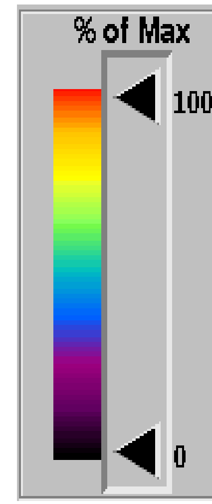




Miconazole Inhibits Defluorination & Bone Uptake

[^{18}F]Fluoride

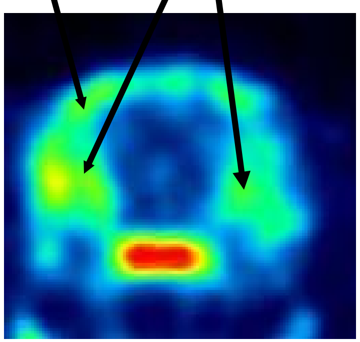




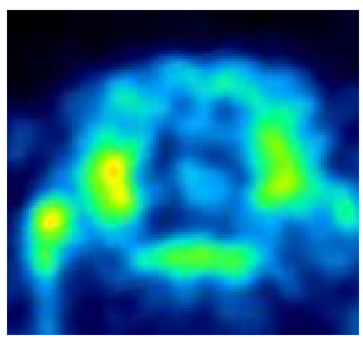
Skull

Temp Ctx

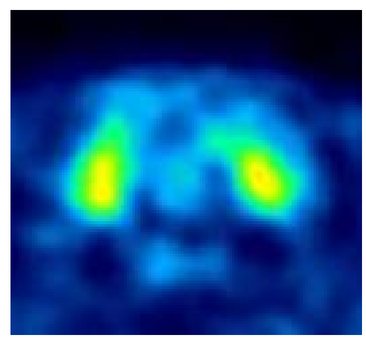
[^{18}F]FCWAY: Miconazole



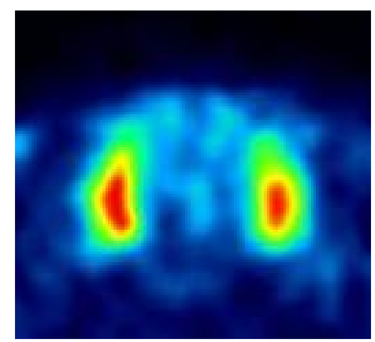
Baseline



15 mg/kg

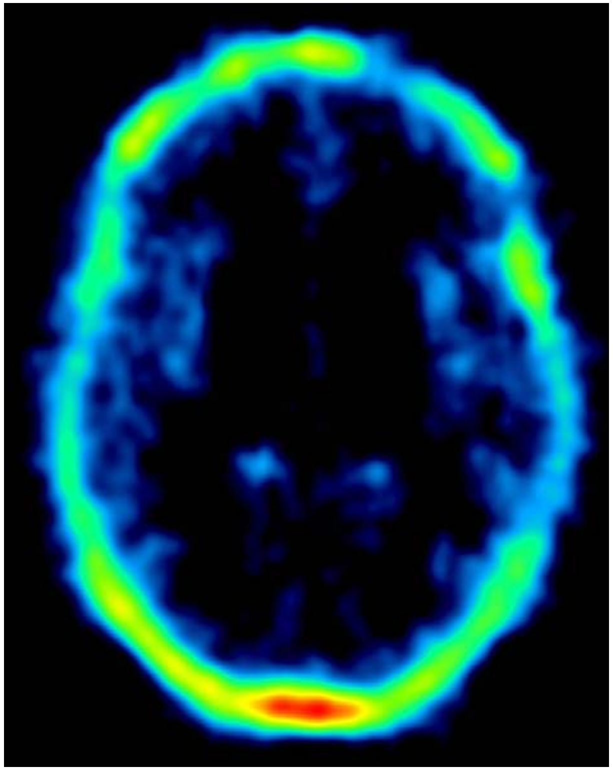


30 mg/kg

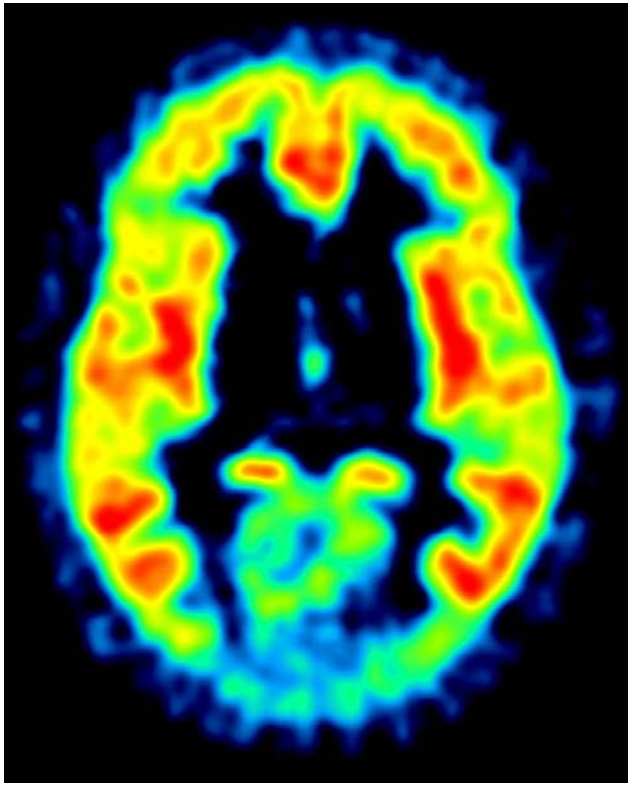


60 mg/kg

Disulfiram: Decreases Skull Activity & Increases Brain Uptake



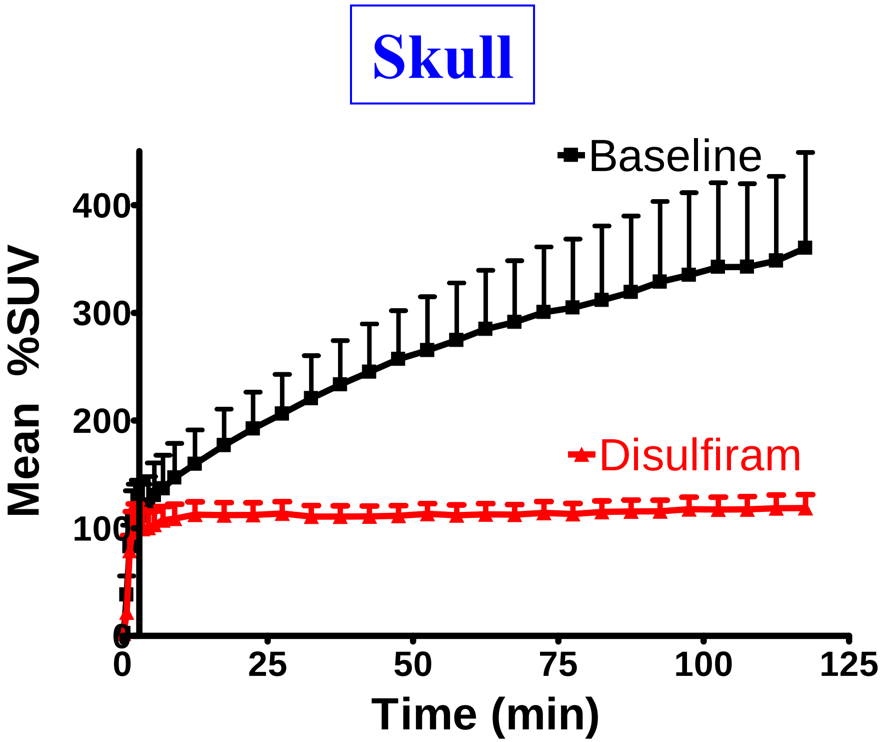
Baseline

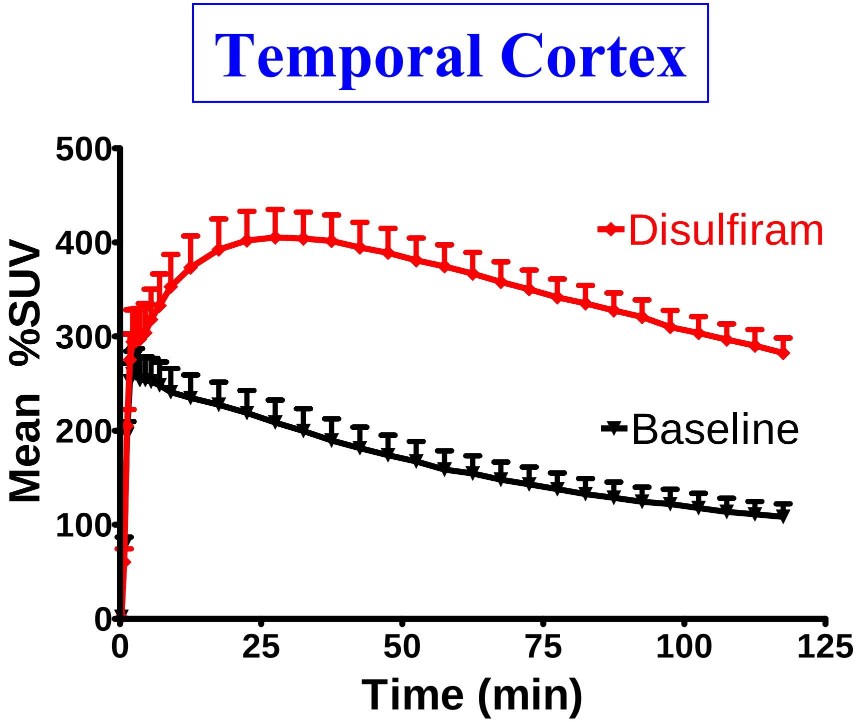


Disulfiram

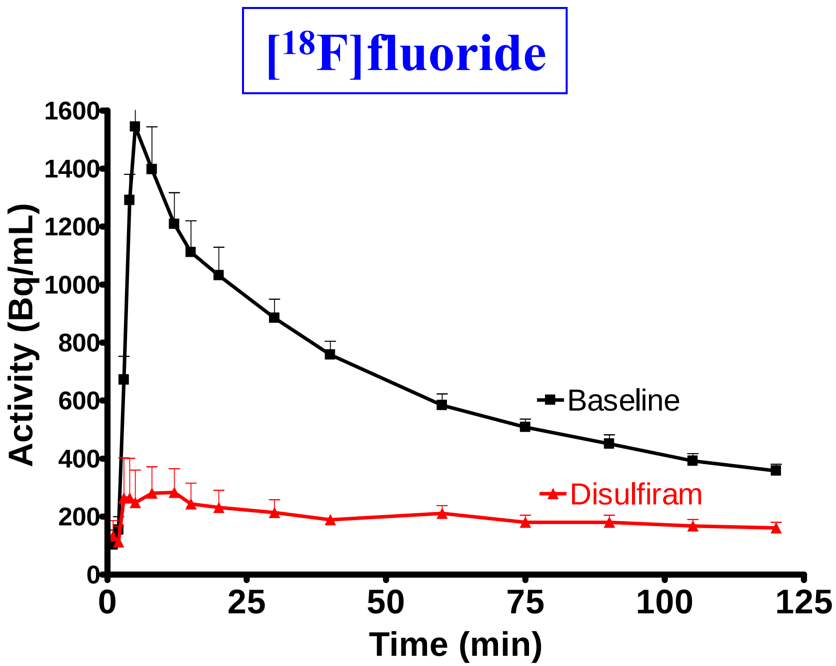
Images at 2 h in same subject. Disulfiram 500 mg PO prior night

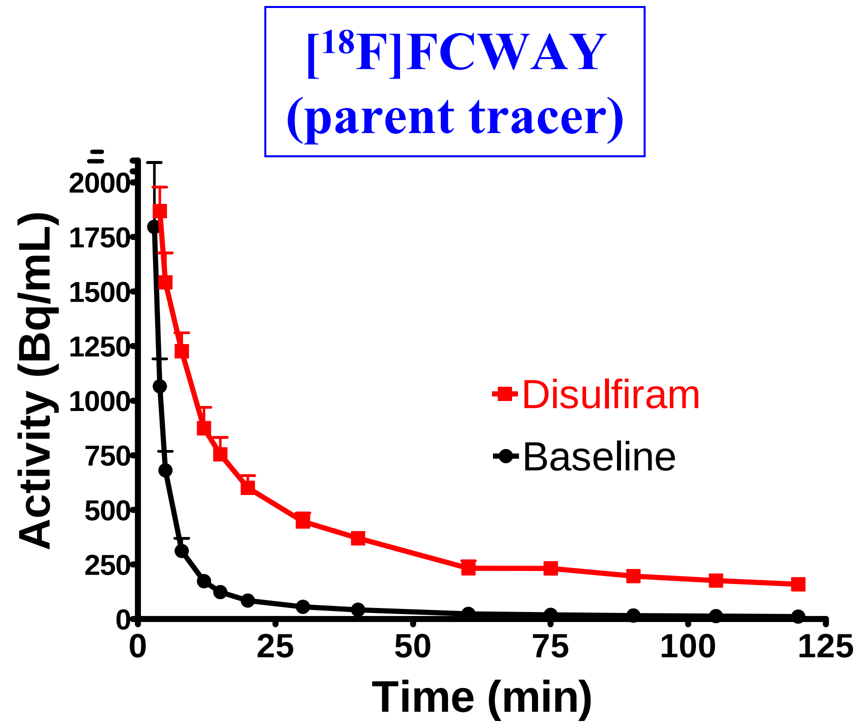
Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of [^{18}F]FCWAY





Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer [^{18}F]FCWAY





Summary of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

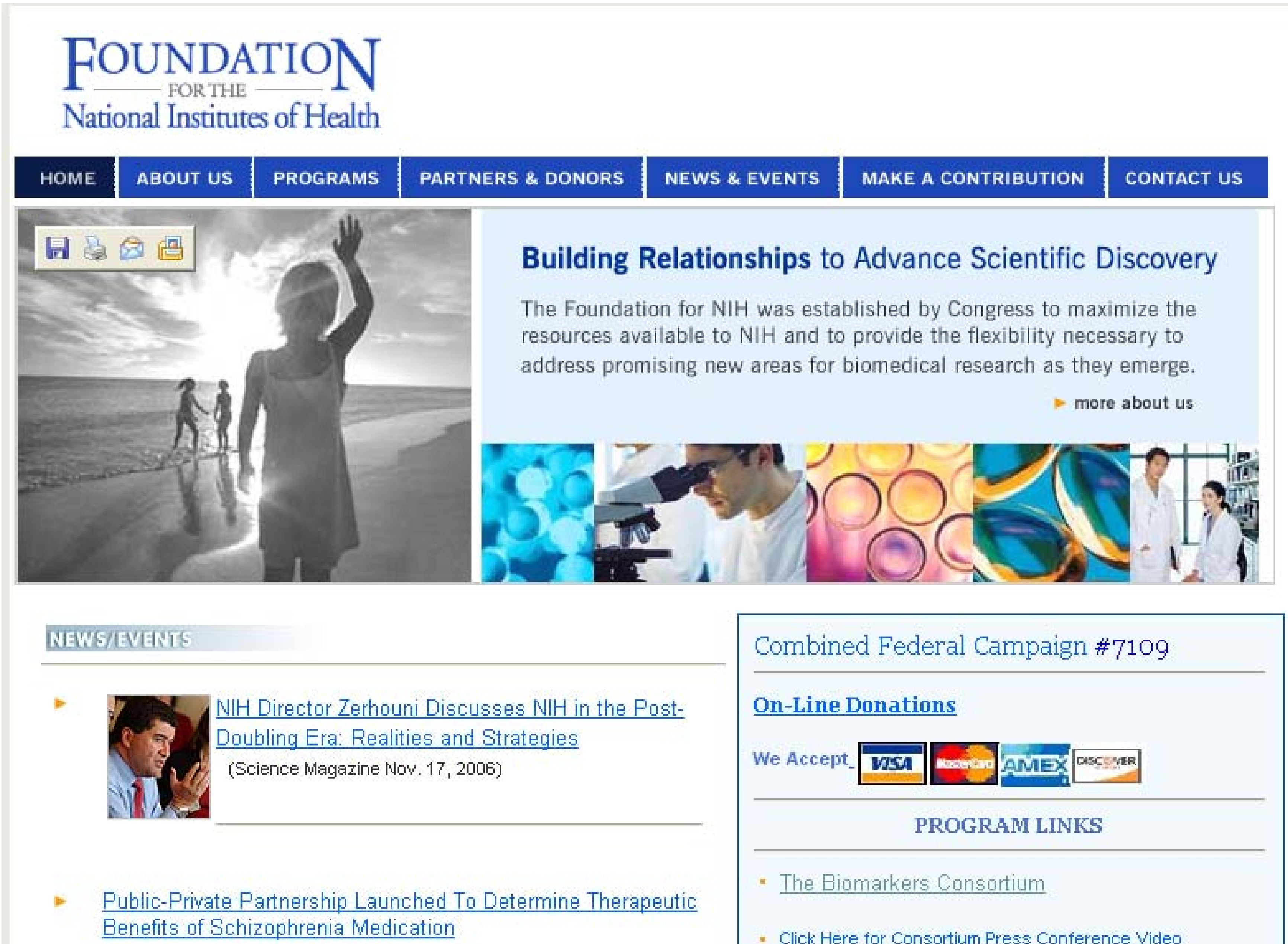
FDA Critical Path Initiative

- Approvals for new drugs declining
- R&D funding by industry and NIH is increasing
- Problem: tools are inadequate for efficient evaluation of new drugs in the “critical path” of development
- Still using old tools like liver enzymes and hematocrit to evaluate safety and efficacy
- Need new **Product Development Toolkit**

<u>CRITICAL PATH</u> to New Medical Products
FDA, March 2004

"There is currently an urgent need for additional **public-private collaborative work** on applying technologies such as … new imaging technologies.

Opportunity: **Imaging technologies**, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals."


FOUNDATION FOR THE National Institutes of Health
HOME
ABOUT US
PROGRAMS
PARTNERS & DONORS
NEWS & EVENTS
MAKE A CONTRIBUTION
CONTACT US
Building Relationships to Advance Scientific Discovery
The Foundation for NIH was established by Congress to maximize the resources available to NIH and to provide the flexibility necessary to address promising new areas for biomedical research as they emerge.
more about us
NEWS/EVENTS
NIH Director Zerhouni Discusses NIH in the Post-Doubling Era: Realities and Strategies
(Science Magazine Nov. 17, 2006)
Public-Private Partnership Launched To Determine Therapeutic Benefits of Schizophrenia Medication
Combined Federal Campaign #7109
On-Line Donations
We Accept
VISA
AMEX
DISCOVER
PROGRAM LINKS
The Biomarkers Consortium
Click Here for Consortium Press Conference Video

THE
BIOMARKERS CONSORTIUM

HOME PAGE

- Public & Private Partners
- Policies and Procedures
- Project Concept Submission
- FNIH Press Release
- HHS Press Release
- Backgrounder
- Executive Committee
- Experts & Leaders Say
- Consortium Fact Sheet
- FDG-PET Fact Sheet
- FDG-PET Experts Say
- Media Contacts

THE BIOMARKERS CONSORTIUM
ADVANCING MEDICAL SCIENCE

The Biomarkers Consortium is a public-private biomedical research partnership of the Foundation for the National Institutes of Health, Inc. that involves a variety of public and private stakeholders including the National Institutes of Health (NIH); Food and Drug Administration (FDA); Centers for Medicare & Medicaid Services (CMS); the pharmaceutical, biotechnology, diagnostics, and medical device industries; non-profit organizations and associations; and advocacy groups (News/Events).

The Consortium will search for and validate new biological markers—biomarkers—to accelerate dramatically the competitive delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state. For example, cholesterol and blood pressure are perhaps the most well known biomarkers; these biomarkers are indicators of cardiovascular health.

Self-Assessment Quiz: True or False?

- Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.